SACHRP Recommendation on Protocol Deviations

A problematic area in human subject protection is the wide divergence among institutions, sponsors, investigators and IRBs regarding the definition of and the procedures for reviewing protocol deviations.

Focus of the Recommendation

In virtually every research study departures occur from the procedures set forth in the IRB-approved protocol. Various terms are used to describe these departures, including "protocol deviations," "protocol violations," "protocol variances," and "non-compliance." For the purposes of this recommendation, such departures shall be herein referred to as "protocol deviations." Protocol deviations occur for a variety of reasons, such as an investigator's decision to deviate from the protocol, the subject's lack of adherence to the protocol, or external/environmental factors (e.g., severe weather or holidays) that change the performance of a protocol. Some protocol deviations are anticipated and/or intentional; others are not. Some protocol deviations are known or identified before they occur; others are only discovered to have occurred after the fact. The HHS and FDA regulations and guidance are inconsistent in addressing protocol deviations, and even among the various FDA regulations and guidance documents there are inconsistencies. However, as noted below in its central recommendation, SACHRP believes that FDA and OHRP can provide guidance to clarify their currently existing positions on this issue.

This recommendation specifically addresses three types of deviations:

- Deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol.
- Deviations from the protocol that are identified before they occur, but cannot be prevented.
- Deviations from the protocol that are discovered after they occur.

Each of these deviations is defined and examples are provided is sections II, III, and IV below. Section V contrasts two other activities from the three types of deviations. These other two activities are:

- Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4).
- Changes in research made in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4).

Both of these activities are outside of the scope of this recommendation.

Section VI provides SACHRP's secondary recommendations regarding the three types of deviations.

I. Current FDA and OHRP Interpretation, and SACHRP's Central Recommendation

The HHS and FDA regulations are inconsistent in addressing protocol deviations. In addition, among the various FDA regulations and guidance there are inconsistencies. However, FDA and OHRP have each indicated in various formats that intentional protocol deviations are changes in research that need prior IRB review and approval. SACHRP's central recommendation is that FDA and OHRP publish a clear statement of their positions regarding intentional protocol deviations. The following are the essential statements of the current FDA and OHRP positions on protocol deviations. (See Appendices I and II for additional background information on existing regulations and guidance.)

FDA Center for Device and Radiologic Health (CDRH):

FDA device regulations explicitly address protocol deviations. 21 CFR 812.150 requires:

> (a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:
> ...
> (4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. ... Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required.

FDA Center for Drug Evaluation and Research (CDER):

FDA drug regulations do not explicitly address protocol deviations. However, the issue is directly addressed in the FDA "Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008." The manual states:

> Protocol deviations. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to

complete scheduled visits as required by the protocol, would be considered protocol deviations. Determine whether changes to the protocol were:

i. Documented by an amendment, dated, and maintained with the protocol;
ii. Reported to the sponsor (when initiated by the clinical investigator); and
iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

Office for Human Research Protections (OHRP):

OHRP has not issued written guidance on protocol deviations. However, OHRP's unwritten position is that all intentional protocol deviations are changes in research that need prior IRB review and approval before implementation.

At the current time, much of the regulated community is unaware of these positions. SACHRP's central recommendation is that FDA and OHRP issue either joint guidance, or if that is not feasible, separate consistent guidance clearly outlining these positions.
The remainder of this letter contains discussion points and references for FDA and OHRP consideration, and minor recommendations on specific points.

II. Intentional Protocol Deviations

The first focus of this recommendation is deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol. Examples of such intentional protocol deviations include the following types of cases:

- Lab criteria: One test is out of range for a benign reason (increased alkaline phosphatase, LDH or SGOT in a runner, or increased bilirubin in a person with Gilbert Syndrome). The investigator decides to enroll the subject despite the out-of-range lab criteria.

- Age criteria: The criteria includes an age requirement of 20-60 years of age, but a potential subject turned 61 a week before screening. The investigator decides to enroll the subject despite being outside of the age range.

- Payment: The protocol specifies that subjects will be paid twenty dollars per visit. To compensate for higher expenses, the investigator decides to pay certain subjects more than other subjects.

- Timing of study visit: At the time of enrollment, the investigator realizes that due to a planned vacation the subject will miss one out of 12 regularly scheduled two-week study visits. The investigator decides to enroll the subject despite this knowledge.

- Timing of washout: A planned vacation interferes with a washout period. Shortening the wash-out period from 14 to 12 days will allow the subject to be enrolled. The investigator decides to enroll the subject with a 12-day washout.

- Pre-treatment exceeded: Protocol entry criteria specify that only a certain amount of pre-treatment of disease is acceptable. A potential subject has exceeded it to a minimal extent. The investigator enrolls the subject despite knowledge of the extent of the pre-treatment.

- Changes to survey instrument: In a behavioral study utilizing a questionnaire, the investigator realizes that two of the questions would work better in reverse order. The investigator re-orders the questions without IRB approval.

In these situations, the investigator or another party decides to deviate from the protocol. Sometimes these intentional protocol deviations are a one-time event. Other times they lead to the implementation of a permanent change to the protocol or other research documents. These intentional protocol deviations may or may not adversely affect the safety, rights and welfare of the research subject, and they may or may not adversely affect the scientific validity of the research.

III. Protocol deviations that are identified before they occur, but cannot be prevented

The second topic of focus for this recommendation is deviations from the protocol that an investigator, research staff and/or other party involved in the conduct of the research are able to identify before they occur, but cannot prevent from occurring. An example is a research subject who is on a business trip and calls the investigator to announce that she is stuck in a snow storm and cannot be at a study visit scheduled for the next day. The investigator knows in advance that the deviation will occur, but it is not under the investigator's control, and it is not the investigator's intent to deviate from the protocol. (See point V.5 below).

IV. Protocol deviations that are discovered after they occur

The third topic of focus for this recommendation is deviations from the protocol that occur because an investigator, research staff and/or other party involved in the conduct of the research deviate from the protocol unintentionally, and such deviations are not identified until after they occur. Examples include an investigator's accidental failure to perform a protocol-required physical, a subject's failure to self-administer or incorrectly administer the test agent, or a coordinator's accidental failure to perform a protocol-required blood test on subjects. These deviations from the protocol were not planned nor intended. These types of deviations must be analyzed upon discovery such that a determination may be made as to the root cause of the deviation, and whether or not such a deviation(s) constitutes an unanticipated problem involving risks to subjects or others and/or constitutes serious or continuing non-compliance.

V. Protocol deviations to eliminate apparent immediate hazards and IRB-approved changes in research

The three protocol deviations described in Sections II-IV that are the focus of this recommendation need to be contrasted from deviations to eliminate apparent immediate hazards

and from IRB-approved changes in research. Both of these activities are already addressed in the regulations and IRBs are required to have written procedures addressing these activities.

Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4): These differ from the protocol deviations as described in the examples above in that these types of deviations are performed in reaction to a perceived hazard, such as the occurrence of an unexpected serious adverse event. They are intentional, but they are done to prevent harm to subjects in a time-sensitive situation, as specifically allowed by the regulations. Thus, they are distinct from the intentional deviations that are the focus of this recommendation.

IRB approved changes in research under 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4): In addition, the protocol deviations that are the focus of this recommendation also need to be contrasted from IRB-approved changes in research. If an intentional protocol deviation is implemented with appropriate review and approval by an IRB and, when applicable, by the sponsor, then it is a change in research as allowed under the regulations at 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4) rather than a protocol deviation. If it is implemented without such review and approval, then it is an intentional protocol deviation.

VI. Recommendations

Consistent with section I above, SACHRP recommends that OHRP and FDA issue a joint guidance, or if that is not feasible consistent guidance, on the procedures for handling protocol deviations. The guidance should ensure the adequate protection of subject safety and integrity of the study while taking into account the burden on investigators and IRBs. The following points should be addressed:

1. The guidance should reinforce the responsibility of investigators and research staff to follow the written protocol as provided by the sponsor and approved by the IRB. Strict adherence to the protocol is more likely to protect human subjects and preserve the integrity of the data and research.

2. The guidance should encourage sponsors and investigators to develop protocols that include flexibility in research methods where possible without adversely affecting subject safety or science. Flexibility that is built into the protocol will reduce the number of changes that have to be reviewed by the IRB and should reduce the number of incidents of deviations and non-compliance by investigators.

3. The guidance should require that permanent changes to protocols be submitted to the IRB as changes to previously approved research for review and approval prior to initiation. This recommendation is consistent with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4). If a modification is minor, it may be reviewed by the expedited procedure or the convened IRB. When applicable, such changes should also have prior sponsor review and approval. Permanent changes to the protocol that are administrative in nature and have no material effect on the regulatory criteria for approval of research, such as a change in telephone number, may be handled outside the IRB process (i.e., by IRB staff).

This is consistent with Section E of the current OHRP "Guidance on IRB Approval of Research with Conditions," which states the following: "*Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research.*"

4. The guidance should also address one-time intentional protocol deviations that are not intended as a permanent change to the protocol. The guidance should state that these deviations are changes to the research that require IRB review and approval, and when applicable approval by the sponsor, before the investigator may implement them. These deviations will commonly qualify for expedited review by the IRB. This is SACHRP's central recommendation, as noted above.

5. The guidance should address the administrative procedures and regulatory status when investigators implement one-time intentional protocol deviations without IRB approval. The guidance should address whether this always constitutes non-compliance with the IRB regulations that must be reported to the IRB. The IRB should determine whether reported intentional protocol deviations affect the criteria for approval of research found at 45 CFR §46.111 and 21 CFR §56.111, and evaluate such deviations according to the IRB's policies and procedures for handling non-compliance and considering whether the deviation constitutes an unanticipated problem involving risks to subjects or others. For research under FDA regulations, the sponsor should also be notified and evaluate the deviation according the sponsor's policies and procedures for handling non-compliance. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

6. The guidance should explicitly distinguish the three types of protocol deviations described in Sections II-IV above. The guidance should also distinguish the three types of deviations from deviations to eliminate apparent immediate hazards and from IRB-approved changes in research.

7. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are identified before they occur, but cannot be prevented*. The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. The investigator should evaluate whether these types of protocol deviations are an unanticipated problem involving risks to subjects or others that needs to be promptly reported to the IRB. Because these protocol deviations are identified before they occur but cannot be prevented, it will usually not be appropriate to submit these deviations to the IRB for prior review and approval as a change in research for two reasons. First, the IRB may decide not to approve the deviation, and second, the IRB may not be able to review the reported deviation prior to its occurrence. Both of these circumstances leave the investigator in the position of not having IRB approval to implement a deviation that the investigator cannot prevent. For research under FDA regulations, the investigator

should also inform the sponsor immediately, and the sponsor should also evaluate these protocol deviations as part of its monitoring duties, and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

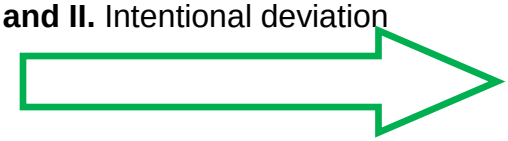
8. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are discovered after they occur*. The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. For research under FDA regulations, the sponsor should also evaluate these protocol deviations as part of its monitoring duties and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events." It will be particularly important for the agencies to balance the burden on investigators and IRBs versus the protection of subject safety and scientific integrity when considering this issue.

9. The guidance should state that IRBs need written policies and procedures addressing the three types of protocol deviations described in Sections II through IV above. The guidance should highlight any areas where IRBs may exert flexibility in defining and determining which changes must be reported to them. For purposes of clarity, the guidance should also explicitly distinguish the two types of protocol deviations outlined in Section V above.

10. SACHRP recognizes that many institutions and IRBs currently do not have policies and procedures in place for reporting and/or handling the three types of protocol deviations described above. The issuance of guidance that only addresses points #3 - #9 above is likely to significantly increase the burden on IRBs. Thus, it is important that there is appropriate emphasis placed on points #1 and #2 above, both in guidance for IRBs, education for investigators, and through dissemination of best practices. For example, it would be extremely helpful to the research community for FDA and OHRP to each identify and publish, in a consistent manner, examples of how to incorporate flexibility into protocols, education programs that help increase compliance of investigators, and models IRBs can use to manage protocol deviations.

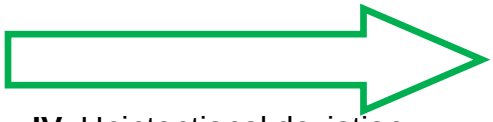
Appendix I

I and II. Intentional deviation



III. Unintentional deviation that can't be prevented

X EVENT



IV. Unintentional deviation discovered after the fact

V. Intentional deviation to prevent harm

V. Traditional change in research, with changes to written documents

Axis: time

Appendix II

Background - Existing Regulations and Guidance

The HHS and FDA regulations are inconsistent in addressing protocol deviations. Even among the various FDA regulations there are inconsistencies. FDA regulations and ICH-GCP requirements are inconsistent. These inconsistencies leave IRBs, sponsors, and investigators with no clear direction on how to handle protocol deviations. The HHS regulations only use the term "changes in a research activity," and state that the only changes that do not need prior IRB review are those that are "necessary to eliminate apparent immediate hazards to the subject." The term "deviation" does not appear in the HHS regulations. OHRP has not issued any written guidance on protocol deviations or on the definition of a change in research. However, OHRP's stated position is that any deviation from a protocol is a change in research that needs prior IRB review and approval.

The FDA regulations and ICH guidance both use the term "deviation" in addition to "changes in a research activity" in various sections. However, the use is not consistent among the three sets of FDA regulations (21 CFR §56, §312, and §812); nor is it consistent between the FDA regulations and the ICH guidelines. The FDA regulations pertaining to IRBs are similar to the HHS regulations pertaining to IRBs, in that, they only address "changes in research activity." However, the ICH-GCP, adopted by FDA as guidance, uses the term "deviations," and requires that IRB procedures specify "that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s))." Unfortunately, the guidance only provides examples of minor changes that do not need prior IRB review. It does not provide examples of minor deviations that do not need prior IRB review.

The FDA regulations pertaining to investigational drugs (21 CFR §312) are similar to the FDA regulations pertaining to IRBs, in that, the regulations themselves only use the term "changes in research," but do not use the term "deviation." However, as with the FDA ICH-GCP, the guidance for investigators does use the term "deviations" in a similar fashion to the ICH guidance for IRBs. The ICH states, "The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s))." As with the ICH IRB guidance, examples of minor changes to the protocol that do not need prior IRB review are provided, but examples of minor deviations that do not need prior IRB review are not provided.

Finally, the FDA ICH guidance has a section addressing the monitoring responsibilities, which is not internally consistent in regards to deviations. In §5.18.4, among the monitor's

responsibilities is "Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations." However, §5.18.6 states that monitors should report *significant* deviations in monitoring reports: "Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance." Minor deviations are not addressed and "significant" is not defined.

The FDA device regulations (21 CFR §812) are different from the FDA IRB and drug regulations, ICH guidance, and the Common Rule, in that, they specifically describe deviations from the protocol that do not require prior IRB review, and also address the role of the sponsor and FDA in regard to these deviations. The device regulations say, "prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required."

Appendix III

HHS Regulation

> §46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
> (b) … Assurances applicable to federally supported or conducted research shall at a minimum include:
> (4) Written procedures which the IRB will follow
> ...
> (iii) for ensuring prompt reporting to the IRB of proposed* changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
> **This word is not in FDA regulations.*

OHRP has not issued written guidance on protocol deviations. However, OHRP's unwritten position is that all planned protocol deviations are changes in research that need prior IRB review and approval before implementation.

FDA Regulations and Guidance - IRBs

> 21 CFR §56.108 IRB functions and operations. In order to fulfill the requirements of these regulations, each IRB shall:
> (a) Follow written procedures:
> ...
> (3) for ensuring prompt reporting to the IRB of changes in research activity; ...
> (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

FDA Regulations and Guidance - Drugs

> 21 CFR §312.30 Protocol amendments
>
> (b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
>
> (i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

21 CFR §312.53 Selecting investigators and monitors.
(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:
(1) A signed investigator statement (Form FDA-1572) containing:
(vii) A commitment by the investigator that, ... the investigator will promptly report to the IRB all changes in the research activity ... and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

21 CFR §312.66 Assurance of IRB review.
... The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

FDA Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008.
Protocol deviations**.** A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally

communicated to FDA. “Protocol deviation” is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. Determine whether changes to the protocol were:

iv. Documented by an amendment, dated, and maintained with the protocol;
v. Reported to the sponsor (when initiated by the clinical investigator); and
vi. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

FDA Regulations and Guidance - Devices

21 CFR §812.35 Supplemental applications.

(a)Changes in investigational plan --(1) Changes requiring prior approval. Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under 812.30(a), and IRB approval when appropriate (see 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan.

(2)Changes effected for emergency use. The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see 812.150(a)(4)).

(3)Changes effected with notice to FDA within 5 days. A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i)Developmental changes. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii)Changes to clinical protocol. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the

protocol;

(B) The scientific soundness of the investigational plan; or

(C) The rights, safety, or welfare of the human subjects involved in the investigation.

21 CFR §812.150 Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:
...
(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. ... Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with §812.35(a) also is required.

FDA Regulations and Guidance - ICH-GCP (E6)
ICH sections 1.45, 3.3.7, and 4.5.2

General Principles

§1.45 Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

IRB

§3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

§3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

Investigator

§4.5 Compliance with Protocol

§4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

§4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

§4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

§4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

§5.18.4 Monitor's Responsibilities

The monitor(s), in accordance with the sponsor’s requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:…

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

§5.18.6 Monitoring Report

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.